CME Article

Opportunistic Infections in Hiv–Aids

Pneumocystis Carinii Pneumonia and Myocbacterium Avium Complex in Hiv-Infected Adults

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Learning Objectives

i. To understand the importance of prevention and treatment of opportunistic infections in hiv–aids patients.
ii. To describe when to start prophylaxis for *Pneumocystis carinii* pneumonia (pcp) and *Mycobacterium avium* complex (mac).
iii. To know which antimicrobial agents to prescribe for pcp and for mac prophylaxis.

Introduction

Remarkable progress has been made over the past twenty years in the treatment of patients with human immunodeficiency virus (hiv) disease. Improvements during the first decade of the hiv pandemic were related to improved recognition of opportunistic infections (ois), improved treatment for acute and chronic complications, and the introduction of chemoprophylaxis against key ois. During the second decade of the pandemic, extraordinary progress has been made in the development of highly active antiretroviral therapies (haart).[1]

Haart is the most effective approach to preventing ois and should be considered for all hiv-infected persons who are medically eligible for such therapy. However, some patients are not ready or able to take haart, and others have tried haart regimens but therapy failed.[1,2] Such patients will benefit from prophylaxis against ois. In addition, prophylaxis against specific ois continues to provide survival benefits even among persons who are receiving haart.[1]

One change in preventing ois in the haart era is the ability of haart to restore immune function. Although the timing of initiating oi prophylaxis continues to be accurately indicated by cd4+ t-lymphocyte counts, a strategy of stopping primary or secondary prophylaxis for certain patients whose immunity has improved as a consequence of haart is now recommended in some instances. Stopping prophylactic regimens can simplify treatment, reduce toxicity and drug interactions, lower cost of care, and potentially facilitate adherence to antiretroviral regimens.[1]

This paper focuses on the most recent recommendations for prophylaxis, diagnosis, and treatment of two important ois, *Pneumocystis carinii* pneumonia (pcp) and *Mycobacterium avium* complex (mac). Inexpensive, easy to use medications are available to prevent and treat both pcp and mac.

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It is important to make sure that all patients who might benefit from these medications are receiving them.

Pneumocystis carinii pneumonia (*P. jiroveci*) PCP

PCP is an acute to subacute, often fatal pulmonary disease. It occurs in high-risk patients, including the chronically ill, malnourished, and immunosuppressed. Impaired cellular immunity has long been considered to be an important predisposing factor in the development of PCP, and, as such, it remains a major opportunistic infection and an indicator disease for AIDS. It has been found to be the leading cause of interstitial plasma cell pneumonia in HIV patients.[2] It affected about 60%–75% of AIDS patients prior to the routine use of prophylactic medications and, subsequently, its incidence has fallen to <15%.[3] Untreated pneumocystosis causes progressive respiratory insufficiency that leads to death. Prognosis is related to the degree of hypoxemia when the patient presents. An arterial oxygen pressure of 70mm hg or more on room air indicates more serious pneumocystosis. The grading system using the alveolar-arterial oxygen gradient is <35 mm hg for moderate disease, 35–45mm hg for moderate disease, and >45 mm hg is indicative of severe disease.[4] The mortality rate of PCP in immunocompromised patients ranges from 5%–40%, if treated, but approaches 100% if untreated.[3]

The etiologic agent of PCP is *Pneumocystis jiroveci*, formerly known as *Pneumocystis carinii*, however, the acronym remains PCP, despite the change in species name. The DNA structure analysis classifies PCP as a fungus, but the organism retains several morphologic and biologic similarities to a protozoan. The mode of transmission is thought to be by direct airborne invasion of the respiratory pathway. Once *P. jiroveci* is inhaled, it escapes the defenses of the upper respiratory tract, is deposited into the alveoli, and attaches to the alveolar type I cell.[3,4] Impairment of humoral or cellular immunity may result in unchecked replication, which can lead to pnemocystosis.[4]

Although the incubation period has not been defined, clinical signs and symptoms may occur one or two months after becoming immunosuppressed. Patients with HIV disease have a higher organism burden, but less severe lung damage than uninfected patients. Pneumocystosis is a more subtle disease in HIV patients, who may remain asymptomatic for weeks to months.[4]

Optimal care for patients with PCP depends on prompt diagnosis and therapy. The clinical presentation of PCP is variable. Progressive dyspnea, fever, and nonproductive cough are the major presenting symptoms of PCP, and tachypnea, tachycardia, and cyanosis are invariably noted in the acutely ill patient. Occasionally, patients have sputum production, while hemoptysis and chest pain are rare. Fever is not always present. Scattered rales may be the only auscultatory sign that is present and then in only 30% of the cases. Chest x-ray typically reveals diffuse bilateral interstitial infiltrates extending from the perihilar region. However, atypical chest x-ray manifestations, such as nodules, cavities, pneumatoceles, lyphadenopathy, or effusions may occur. Patients receiving prophylactic aerosolized pentamidine may have apical infiltrates and pneumothoraces on their chest x-ray.[4] On rare occasions the chest x-ray obtained at the time of diagnosis is normal. In cases where the chest x-ray is not definitive, high resolution CT scan will invariably present as a ground-glass appearance in the infiltrated areas.[3]

PCP must be considered in the differential diagnosis of HIV–AIDS patients who present with respiratory symptoms, fever, and an abnormal chest x-ray. Diagnosis is made by histopathologic demonstration of *P. jirovecin* in respiratory secretions. The use of immunoflorescence must be weighed against the need for specialized facilities and higher cost. There is presently no reliable culture or serologic test in routine use.[4]

A frequently used method of specimen collection is induced sputum using a saline mist. This is a noninvasive, simple procedure with a diagnostic yield of 60%–90%. Fiberoptic bronchoscopy is the most commonly performed invasive procedure and

reveals a diagnosis of pneumocystosis in 95% of cases.[4,5] Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) has a better sensitivity and lower morbidity than washings and brushings. BAL conducted with multiple lobes increases the diagnostic yield. In addition, BAL provides information on organism burden, other infectious agents, and inflammatory response that are not available from induced sputum specimens. Transbronchial biopsy poses a greater risk of pneumothorax and bleeding. If bronchoscopy does not provide a diagnosis, open lung biopsy may be helpful. An open lung biopsy can also detect other infectious agents, Kaposi's sarcoma, and conditions complicating pneumocystosis.[4]

The mortality in HIV patients is about 10%–20% compared to 30%–50% in non-HIV patients. Patients who recover from PCP are at risk for the development of recurrent episodes of the disease as long as the immunosupressed condition persists.[4]

Extra pulmonary pneumocystosis occurs mainly in patients with advanced HIV disease who are either on prophylaxis or on aerosolized pentamidine. A survey of autopsies of 233 HIV patients at two medical centers over a twelve-year period published in 1998 revealed evidence of PCP in 24% of patients with extra pulmonary involvement in 13%. The main extrapulmonary sites of involvement are the lymph nodes, spleen, liver, bone marrow, gastrointestinal tract, eyes, thyroid, adrenal gland, and kidney.[4] These reports raise the question as to whether extra pulmonary dissemination of *P. jiroveci* is more common than was once believed.

Clinically, extrapulmonary pneumocystosis can present with or without pulmonary symptoms. Presentation ranges from rapidly progressive multisystem disease to an incidental autopsy finding. Focal presentation includes a rapidly enlarging thyroid mass, pancytopenia, cotton wool spots on the retina, polypoid lesions in the external auditory canal, pleural effusion, hypodense computerized tomography lesions in the spleen, and punctuate calcifications in the spleen, liver, adrenal gland, or kidney. Biopsy or fine needle aspiration shows areas of necrosis filled with foamy material. Gomori methenamine silver, or fluorescent monoclonal antibody stains reveal numerous specific organisms within these necrotic areas. Prophylactic therapy can prevent extrapulmonary PCP and is preferred over aerosolized pentamidine alone.[4]

PROPHYLAXIS

PCP prophylaxis is recommended for patients with a CD4+ T-lymphocyte count <200 cells uL or when the history or symptomatology suggests oral-pharyngeal candidiasis. Persons with a CD4+ T-lymphocyte count of <14% or a history of AIDS defining illness who do not otherwise qualify should also be considered for prophylaxis. When monitoring CD4+ T-lymphocyte counts for more than three months is not possible, initiating chemoprophylaxis at a CD4+ T-lymphocyte count of >200 but <250 cells/uL, should also be considered. Prophylaxis should also be strongly considered in patients with CD4+ T-lymphocyte counts of >200 but <250 u/L.[1]

Sulfamethoxazole/trimethoprim (TMP-SMZ) is the drug of choice for prophylaxis of all forms of pneumocystosis. The preferred regimen is one double-strength tablet daily. However, one single-strength tablet daily may be easier for the patient to tolerate. One double strength tablet three times a week is also effective.[1]

TMP-SMZ is well tolerated by non-HIV patients but, HIV patients experience a high frequency (80%) of adverse reactions that begin in the second week of therapy and may result in the discontinuance of the drug in up to 50% of these persons. Adverse reactions include rash, fever, nausea, vomiting, pruritis, neutropenia, and increased transaminases. Neurologic toxicity may include tremor, ataxia, apathy, and ankle clonus, which seem to disappear rapidly on drug discontinuance.[3,4] If clinically feasible, TMP-SMZ should be continued for patients who have a non-life-threatening adverse reaction. For patients who have stopped TMP-SMZ because of an adverse reaction, reinstitution of TMP-SMZ should be strongly considered after the adverse event has resolved. Patients who have had adverse events, especially fever and rash, might better tol-

erate reintroduction of the drug with a gradual increase in dose (desensitization) or reintroduction of TMP-SMZ at a reduced dose or frequency. As many as 70% of patients can tolerate reinstitution of therapy.[1]

If TMP-SMZ cannot be tolerated, prophylactic regimens that can be recommended as alternatives include dapsone 100mg/day or 50mg orally b.i.d., dapsone 50mg/day plus pyrimethamine 50mg/week plus leucovorin 25mg/week, dapsone 200mg/week plus pyrimethamine 75mg/week plus leucovorin 25mg/week, aerosolized pentamidine 300mg/month using 6mL of diluent delivered from a 50 psi compressed air source administered by the Respirgard II™ nebulizer (Marquest, Englewood, Colorado) with or without 2 whiffs of albuterol to reduce cough and bronchospasm, and atovaquone 1500mg/day orally with meals.[1,5] Atovaquone appears to be as effective as aerosolized pentamidine or dapsone, but it is much more expensive than the other regimens. For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMZ, recommended alternatives to TMP-SMZ for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine or atovaquone with or without pyrimethamine. Some regimens are not recommended because there is insufficient data on their efficacy. These include: aerosolized pentamidine administered by other nebulization devices, intermittently administered parenteral pentamidine, oral pyrimethamine plus sulfadoxine, oral clindamycin plus primaquine, and intravenous trimetrexate. However, these agents may be considered in unusual situations in which the recommended agents cannot be administered.[1]

DISCONTINUING AND RESTARTING PRIMARY PROPHYLAXIS

If immune reconstitution does not occur, patients should be on PCP prophylaxis for life. However, discontinuing therapy of prophylaxis should be considered if there is an increased CD4+ T-lymphocyte count to >200 cells/uL for three months or more. Discontinuance of primary prophylaxis should be considered because it adds limited disease prevention, and it reduces pill burden, drug toxicity potential, adverse drug interaction, selection of resistant pathogens, and costs. Prophylaxis should be reintroduced if the CD4+ T-lymphocyte count falls below 200 cells/uL.[1]

Discontinuance of secondary prophylaxis (chronic maintenance therapy) has the same positive aspects as those seen in the discontinuance of primary prophylaxis. Continuance of prophylaxis apparently adds limited disease prevention for PCP, toxoplasmosis, or bacterial infections when the CD4+ T-lymphocyte count has increased from <200 to >200 cells/uL. Secondary prophylaxis should be restarted when the CD4+ T-lymphocyte count decreases to <200 cells/uL or if PCP reoccurred at a cell count >200 cells /uL.[1]

The preferred regimen for treatment of PCP is two double strength TMP-SMZ t.i.d. For mild disease with a rapid response, treatment may only require 14 days. Patients with moderately severe or severe PCP with hypoxemia (PO_2 <70mm Hg or A-a gradient >35 mm Hg should receive corticosteroids (prednisone 40 mg PO b.i.d for 5 days, then 40 mg daily for 5 days, then 20 mg/day to completion of treatment). Intravenous methylprednisolone can be given at 75% of the prednisone dose. Alternative treatment regimens include TMP 15 mg/kg/day + dapsone 100mg/day orally for 21 days, pentamidine 3–4mg/kg/day IV infused over 60 minutes or longer for 21 days, clindamycin 600–900mg IV every 6–8 hours or 300–450mg orally every 6 hours with primaquine 15–30mg/day orally for 21 days, atovaquone 750 mg suspension orally b.i.d with meals for 21 days, or trimetrexate 45mg/m^2/day intravenous plus leocovorin 20 mg/m^2 orally or intravenous every 6 hours with leucovorin for 3 days longer than trimtrexate.[5]

PROPHYLAXIS DURING PREGNANCY

PCP prophylaxis should be given to pregnant women as is done for other adults and adolescents. TMP-SMZ is the recommended prophylactic agent; dapsone is an alternative. Because of theoretical concerns about possible teratogenicity associated with drug exposures during the first trimester, phy-

sicians may choose to withhold prophylaxis during the first trimester. In such cases, aerosolized pentamidine may be considered, because it is not absorbed systemically and, therefore, does not expose the developing embryo to the drug.[1]

TREATMENT

Treatment response is slow, usually taking 5–7 days. Therefore, the preferred treatment of TMP-SMZ should not be changed on the assumption that there is a clinical failure until there has been at least five days of treatment. Unfortunately, some patients do not respond to any therapy. Patients requiring hospitalization for PCP have a mortality of 15%–20%.[5]

MYCOBACTERIUM AVIUM COMPLEX (DISSEMINATED MAC DISEASE)

Prior to the availability of potent antiretroviral therapy (ART), disseminated MAC was the most common bacterial complication of AIDS. It occurred in up to 43% of AIDS patients. The advent of HAART has markedly reduce disseminated MAC in AIDS patients.[6]

MAC is actually a combination of *Mycobacterium avium* and *Mycobacterium intracellulare*.

These are nontubercular bacterial members of the mycobacteria (*Bacillus*) family that cause a pulmonary disease of indolent cavitation and disseminated disease in patients with a lowered immune response.[6,7] Although found in water, soil, dust, animals, and certain food products, there are no specific recommendations for exposure avoidance.[1,6] Environmental sources may be the source of most human infections, with the majority of cases probably caused by inhalation or ingestion of MAC by patients with immunodeficiency. There is no known evidence of person-to-person transmission of MAC.[6]

The epidemiology of MAC has been poorly delineated to date, but it is thought to be very similar to that seen with the *Mycobacterium tuberculum* species. An incubation period of 2–4 weeks, although variable, is thought to be generally accurate, but it is normally accelerated in the immunocompromised patient.[6,7]

Risk factors for disseminated MAC in AIDS patients include previous opportunistic infections, HAART interruption, anemia at the time of an AIDS-defining condition, and a low CD4+ T-lymphocyte count.[6]

Unlike the case with non-AIDS patients, the lung is an unusual site of MAC in AIDS patients. The diagnosis of MAC requires a combination of compatible signs and symptoms with organism isolation. The physical examination does not provide any pathognomonic findings.[6] The classic signs and symptoms of disseminated MAC in AIDS patients are fever, drenching night sweats, and weight loss. Anorexia also occurs frequently. Nausea, vomiting, watery diarrhea, and abdominal pain are seen with gastrointestinal involvement, and they are thought to be due to intestinal lymphadenitis. Profound anemia may require transfusion. Widesperead involvement of the reticuloendotheial system may result in hepatomegaly, splenomegaly, and lymphadenopathy. Rales are frequently present following the early respiratory symptoms, and a developing productive cough is not unusual.[6]

The diagnosis of pulmonary MAC requires an infiltrate on chest x-ray with a positive sputum culture showing 2+ or greater growth, and at least one positive acid fast bacillus (AFB) stain that is 2+ or greater, or a positive culture and multiple positive smears.[5,6] Because colonization may occur, the presence of MAC in an isolated sputum specimen does not indicate disease.[6] Disseminated MAC is diagnosed by a positive nonpulmonary culture from a normally sterile site.[5] Blood cultures are 90%–95% sensitive in diagnosing disseminated MAC in AIDS patients, but they frequently require 7–14 days. Diagnosis of disseminated MAC rarely requires a biopsy of the liver, bone marrow, or lymph nodes.[5,6]

The differential diagnosis of MAC in a patient with advanced HIV disease includes AIDS wasting syndrome, cytomegalovirus, eneteric bacteremia, fungal disease, *Mycobacterium genevense* infection, and *mycobacterium tuberculosis* infection.

PROPHYLAXIS

Before starting prophylaxis, disseminated MAC disease should be ruled out through clinical assessment, which might include obtaining a blood culture for MAC if warranted. Because treatment with rifabutin could result in the development of resistance to rifampin in persons who have active tuberculosis, active tuberculosis should also be excluded before rifabutin is used for prophylaxis.[1]

Although the detection of MAC organisms in the respiratory or gastrointestinal tract might predict the development of disseminated MAC infection, there are no data available on the efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs in patients with MAC organisms at these sites and a negative blood culture. Therefore, routine screening of respiratory or gastrointestinal specimens for MAC cannot be recommended.[1]

Initiating primary chemoprophylaxis against MAC should be considered if the patient has a CD4+ T-lymphocyte count of <50 cells/uL.[1,3,5,8]

Clarithromycin (500 mg by mouth/twice each day) or azithromycin (1.2 grams PO, as 1 dose/ week) are the preferred agents. A combination of clarithromycin and rifabutin (300 mg orally once each day) is more effective than clarithromycin alone, but it is associated with a higher incidence of adverse drug reactions. This combination should not be used in prophylaxis. The same is true of azithromycin and rifabutin in combination.[1,3,5,8]

An alternative option for prophylaxis is rifabutin (300 mg. by mouth each day) alone, which may be used in the case of intolerance to clarithromycin or azithromycin, but it should be noted that a high incidence of adverse reactions have been reported and make the management of rifabutin therapy difficult. Other drug interactions have been noted with the use of rifabutin in patients taking protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). All PIs and NNRTIs require a dose adjustment when given with rifabutin.[1,3] An additional option is azithromycin (1.2 grams PO, as 1 dose/week) plus rifabutin (300 mg. by mouth each day).[1,5]

DISCONTINUING AND RESTARTING PRIMARY PROPHYLAXIS

Patients who have responded to HAART with an increased CD4+ T-lymphocyte count to >100 cells/uL for more than three months may discontinue therapy with minimal risk. This action is recommended because prophylaxis does little to prevent MAC or bacterial infections. At the same time, discontinuance reduces pill burden, drug toxicity and interaction potential, drug resistant pathogens, and costs.[1,3]

Primary prophylaxis should be restarted if the CD4+ T-lymphocyte count decreases to <50–100 cells/mL.[1,5]

Preventing recurrence is important. Patients with disseminated MAC should receive life-long maintenance therapy, unless immune reconstitution occurs with ART therapy. If macrolide resistance has not been detected through clinical or laboratory evaluation, the use of a macrolide (clarithromycin or azithromycin) is recommended in combination with ethambutol with or without rifabutin. If selected, clarithromycin should be used at dose of 500 mgs two times each day. Higher doses should not be used, as they result in an increased mortality rate.[1] Clofamazine should not be used, as it is associated with increased adverse clinical outcomes.[1,3]

Discontinuance of secondary (maintenance) prophylaxis should also be accompanied by a blood culture to substantiate that the disease state is no longer active. Patients are at low risk for recurrence of MAC when they have completed a course of >12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have sustained an increase in their CD4+ T-lymphocyte counts to >100 cells/uL for 6 months after HAART.[1]

Secondary prophylaxis should be restarted if the CD4+ T-lymphocyte count decreases to <100 cells/uL.[1,3]

PROPHYLAXIS DURING PREGNANCY

The recommendations for MAC prophylaxis in pregnant women are same as for other adults and adolescents. Because of general concerns about administering drugs during the first trimester of pregnancy, some physicians may decide to withhold prophylaxis during the first trimester. Animal studies and anecdotal evidence of safety in humans suggest that of the available agents, azithromycin is the drug of choice. Experience with rifabutin in pregnant women is limited. Clarithromycin has been shown to be a teratogen in animals and should be used with caution during pregnancy. For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol are the preferred drugs.[1]

TREATMENT

The preferred regimen for treatment of MAC is clarithromycin 500 mg orally b.i.d. plus ethambutol 15/mg/day orally or azithromycin 500–600mg/day plus ethambutol 15/mg/day orally. For severe symptoms the recommended treatment is two of these drugs plus ciprofloxacin 500–750mg orally b.i.d. or levofloxacin 500–750mg orally daily or rifabutin 300 mg/day orally, or amikacin 10–15mg/kg/day IV. Which of these drugs is the best to add as the third drug remains unclear.[5]

Untreated MAC results in progressive clinical deterioration with a median survival time of 2–7 months.[6] Response to therapy is equally slow, and the prognosis is poor without immune reconstitution.[5] The clinical course may become chronic; however, in most instances clinical improvement is noted at 2–4 weeks.[5,6] With HAART, half the patients have sterile blood cultures within 12 weeks. However, 30% of these patients relapsed. The mortality from all causes at 24 weeks is 60%.[5]

CONCLUSIONS

Opportunistic infections can be overwhelming in immunocompromised patients and, particularly, in patients with HIV–AIDS, where rapidly progressive infections may be life threatening. PCP and MAC are two of the more dangerous agents to these patients and must be vigorously guarded against by the practicing physician. Early recognition and treatment are imperative, and their increasing use has produced dramatic success in reducing the infection rate to a level of 50% of that noted prior to the use of prophylaxis therapy.

Prophylaxis in both PCP and MAC infections with medication is both simple and relatively innocuous, thus assuring good patient compliance. Physician compliance with MAC prophylaxis recommendations is only about 50%, as compared to 80% compliance for PCP prophylaxis.[5] Prevention is preferable to treatment.

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CME EXAMINATION DEADLINE: NOVEMBER 30, 2005

1. At which of the following CD4+ T-lymphocyte counts should chempoprophylaxis for *Pneumocystis carinii* pneumonia (PCP) be started in adults?
   a. <50 cells/uL
   b. <100 cells/uL
   c. <150 cells/uL
   d. <200 cells/uL

2. At which of the following CD4+ T-lymphocyte counts should chempoprophylaxis for *Mycobacterium avium* complex (MAC) be started in adults?
   a. < 50 cells/uL
   b. < 100 cells/uL
   c. < 150 cells/uL
   d. < 200 cells/uL

3. Which is the preferred drug regimen for chemoprophylaxis against PCP among HIV-infected adults and adolescents?
   a. Aerosolized pentamidine, 300mg monthly
   b. Autovaquone, 1,500 mg daily
   c. Dapsone, 100 mg daily
   d. Trimethoprim-sulfamethoxazole (TMP-SMZ), 1 double-strength tablet daily

4. Which is the preferred drug regimen for chemoprophylaxis against MAC among HIV-infected adults and adolescents?
   a. Clarithromycin 500 mg twice a day
   b. Clarithromycin 500 mg twice a day + azithromycin 1,200 mg weekly
   c. Rifabutin 300 mg daily
   d. Rifabutin 300 mg daily + azithromycin 1,200 mg weekly

5. Which of the following CD4+ T-lymphocyte counts is an indication to discontinue PCP prophylaxis?
   a. >50 cells/uL
   b. >100 cells/uL
   c. >150 cells/uL
   d. >200 cells/uL